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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/752,659	01/07/2004	Marc Elliot Rothenberg	CMC / 161	4105
26875	7590	01/31/2006	EXAMINER	
WOOD, HERRON & EVANS, LLP 2700 CAREW TOWER 441 VINE STREET CINCINNATI, OH 45202			LEE, BETTY L	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 01/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/752,659	ROTHENBERG ET AL.
	Examiner Betty Lee, Ph.D.	Art Unit 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 21 November 2005.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-50 is/are pending in the application.
 - 4a) Of the above claim(s) 8,12,30 and 35-43 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 1-7, 9-11, 13-29, 31-34 and 44-50 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>9/20/04</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's response filed November 21, 2005 is acknowledged. Applicant's election of Group I, claims 1-34, 44-50 is noted. Claims 8, 12 and 30 are drawn to non-elected species. Claims 8, 12, 30, 35-43 are withdrawn from consideration. Applicant's election of species (item 7) eosinophil function: receptor internalization; (item 8) location of transmigration: lung; (item 9) eosinophil reduced in body part affected by allergy: lung; (item 10) chemoattractant: eotaxin 1; (item 11) route of administration: intranasal; (item 13) negatively affected cytokine: eotaxin 1 is noted.

In response to Applicant's statement that an oral election was made, Applicant's oral election with Examiner Galvez is not present in the official record.

The amendment to the Specification is acknowledged. The amendment to Figures 2A and 2B is noted.

Claims 1-7, 9-11, 13-29, 31-34, 44-50 are under examination.

Claim Objections

Claims 1-4, 9, 10, 15, 16, 20, 22, 29, 32, 33, 46, 48 and 50 are objected to because of the following informalities: The claims encompass nonelected species. Appropriate correction is requested.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 14-23, 27, 28, 44-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting at least one of eosinophil recruitment or eosinophil function by administering monokine induced by interferon γ (MIG) or IP-10 does not reasonably provide enablement for methods of inhibiting at least one of eosinophil recruitment or eosinophil function by administering ALL cytokines with eosinophil recruitment- or function-inhibitory activity; methods of inhibiting at least one of eosinophil recruitment or eosinophil function by administering proteins homologous to MIG or IP-10 or peptides derived from MIG or IP-10 or combinations thereof. Furthermore, while the specification is enabling for inhibiting an eosinophil response to eotaxin-1, eotaxin-2 and IL-13, it is not enabling for ‘inhibiting an eosinophil response to ALL chemoattractants, including eotaxin-3, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, RANTES, MIP-1a, IL-4 or combinations thereof.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The first paragraph of 35 U.S.C. 112 states, “The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...”. The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring “ingenuity beyond that to be expected of one of ordinary

Art Unit: 1647

skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986).

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The instant disclosure fails to meet the enablement requirement for the following reasons:

The nature of the invention: The claimed invention is drawn to a method of inhibiting at least one of eosinophil recruitment or function consisting of receptor expression, receptor internalization, signal transduction, transmigration, desensitization,

Art Unit: 1647

degranulation, mediator release, oxidase activity and combinations thereof, by administering an isolated cytokine with eosinophil recruitment- or function-inhibitory activity in a pharmaceutically effective amount.

The state of the prior art and the predictability or lack thereof in the art: The art teaches that the chemokine eotaxin, may have other activities because its mRNA is constitutively expressed at high levels in multiple tissues in the absence of eosinophilic inflammation (Rothenberg, et al. J. Exp. Med. 185: 785-790, 1997). It has weak macrophage chemoattractive activity at high doses in vitro and the role of eotaxin during eosinophil-mediated disease is unknown (pg 785, col 2). The role of eotaxin in eosinophil recruitment would be complicated by the unpredictability of its other functions. Rothenberg, et al teach that given the large number of chemoattractants that have activities on eosinophils, it is unclear whether eotaxin has an important role *in vivo* or not (pg 785, Abstract).

The amount of direction or guidance present and the presence or absence of working examples: The specification does not disclose any cytokines with eosinophil recruitment- or function-inhibitory activity other than MIG; it does not disclose any proteins homologous to MIG or IP-10, and does not disclose peptides derived from MIG or IP-10. The specification discloses that both MIG and IP-10 are induced by allergens (Fig 1). The specification further discloses a series of experiments showing the effects of MIG on eosinophil migration *in vitro* and *in vivo* (Fig 2 and 4), inhibitory effect of MIG-pretreatment on eosinophil response to eotaxin-2 (Fig 3), effects of MIG on eosinophil recruitment (Fig 5), effects of MIG on eosinophils *in vitro*, effects of MIG on eosinophil

Art Unit: 1647

chemotaxis (Fig 7) and effects of MIG on leukocyte recruitment to the lung induced by IL-13 (Fig 8). The specification fails to provide any guidance to the effects of IP-10, proteins homologous to or peptides derived from MIG or IP-10.

The breadth of the claims and the quantity of experimentation needed: The claims are directed to a broad spectrum of cytokines with eosinophil recruitment- or function-inhibitory activity. However since the art teaches that there is considerable unpredictability in chemokine activity and effects, and in the absence of sufficient guidance in the specification to overcome the teachings of unpredictability found in the art, it would require undue experimentation for a person of skill in the art to be able to practice the invention commensurate in scope with the claims.

Claims 1-7, 14-23, 27, 28, 44-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written

Art Unit: 1647

description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to two genera, i.e. 1) cytokines with eosinophil recruitment- or function-inhibitory activity or lacking eosinophil chemoattraction activity and negatively affecting eosinophil activation activity; 2) proteins homologous to or peptides derived from MIG or IP-10. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states An adequate written description of a DNA ... requires a precise definition, such as by

structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

There are two species of the claimed genera disclosed that is within the scope of the claimed genus, *i.e. MIG and IP-10*. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. There is substantial variability among the species. The specification only describes MIG in great detail and IP-10 to a lesser extent. There is no disclosure of proteins homologous to or peptides derived from MIG or IP-10 in the specification.

One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genera. The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (see *Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1,4, 6, 7, 27, 44, 47 and 48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase 'cytokine is a protein homologous to MIG or IP-10'. It is unclear what is encompassed by the term 'homologous'.

Claims 6 and 7 cite the phrase 'perturbed'. It is unclear how signal transduction is measured or how to determine Erk1 or Erk2 perturbation.

Claim 27 cites 'cytokine capable of negatively regulating an inflammatory cell within a lung'. It is unclear how the regulation of an inflammatory cell is measured or what function is affected negatively. Neither is it clear what the regulation of function is compared to.

Claim 44 cites 'negatively affecting at least one of eosinophil chemoattraction or eosinophil activation activity'. It is unclear what is meant by 'negatively affecting'.

Claims 47 and 48 cite 'cytokine such as eotaxin-1 is negatively affected'. It is unclear what function is negatively affected.

Thus, the metes and bounds of the claimed invention cannot be determined and the claims are indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 9-11, 13-29, 31-33, 44-50 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuna, et al (WO9421277).

The claimed invention is drawn to a method of inhibiting at least one of eosinophil recruitment or function consisting of receptor expression, receptor internalization, signal transduction, transmigration, desensitization, degranulation, mediator release, oxidase activity and combinations thereof, by administering an isolated cytokine with eosinophil recruitment- or function-inhibitory activity in a pharmaceutically effective amount. The invention is also drawn to administering to an individual a pharmaceutical composition comprising an isolated eosinophil-inhibitory cytokine such as MIG, IP-10 or combinations thereof at a dose of 10 µg/kg to 10 mg/kg via an intranasal route for systemic administration to inhibit an eosinophil response to a chemoattractant (eotaxin among others), to alleviate inflammation in an airway or tissue exposed to an allergen which results in allergic rhinitis, asthma, eczema and combinations thereof.

For purposes of the claims as drawn to IP-10, the above reference is anticipatory for IP-10.

Kuna, *et al* teach a method of inhibiting allergic disease, e.g. a respiratory allergic disease in mammals such as humans by administering a therapeutically effective amount of one or more of RANTES, MIP-1 α , MIP-1 β , CTAP-III or IP-10 (pg 7, lines 24-30). Kuna, *et al* teach the treatment of allergic diseases such as asthma by administration via various routes, including inhalation of an aerosol (intrabronchial or intranasal), intranasal drops, injection or topical application to an affected area of skin or eye (pg 22, lines 20-27). Kuna, *et al* teach that inhalation is the preferred method of administration for respiratory allergic diseases such as asthma (oral inhalation) and allergic rhinitis (intranasal inhalation) (pg 22, line 34, pg 23, lines 1-5). Furthermore,

Kuna, *et al* teach the dosage should be in the range of about 0.5 to 500 µg/kg, preferably 20 to 200 µg/kg (pg 24, lines 14-15).

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 14-29, 31-33, 44-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuna, *et al* (WO9421277) in view of Loetscher, *et al* (J. Biol. Chem. 276(5): 2986-2991, 2001) and Kaplan (Int. Arch. Allergy Immunol. 124: 423-431, 2001).

For purposes of the instant rejection, the claims have been interpreted as drawn to a method of inhibiting at least one of eosinophil recruitment or function consisting of receptor expression, receptor internalization, signal transduction, transmigration, desensitization, degranulation, mediator release, oxidase activity and combinations thereof, by administering an isolated cytokine with eosinophil recruitment- or function-inhibitory activity in a pharmaceutically effective amount, wherein the cytokine is MIG, at a dose of 10 µg/kg to 10 mg/kg via an intranasal route for systemic administration to inhibit an eosinophil response to a chemoattractant (eotaxin among others), to alleviate inflammation in an airway or tissue exposed to an allergen which results in allergic rhinitis, asthma, eczema and combinations thereof.

Kuna, *et al* teach a method of inhibiting allergic disease, e.g. a respiratory allergic disease in mammals such as humans by administering a therapeutically effective amount of one or more of RANTES, MIP-1 α , MIP-1 β , CTAP-III or IP-10 (pg 7, lines 24-30). Kuna, *et al* teach the treatment of allergic diseases such as asthma by administration via various routes, including inhalation of an aerosol (intrabronchial or intranasal), intranasal drops, injection or topical application to an affected area of skin or eye (pg 22, lines 20-27). Kuna, *et al* teach that inhalation is the preferred method of administration for respiratory allergic diseases such as asthma (oral inhalation) and allergic rhinitis (intranasal inhalation) (pg 22, line 34, pg 23, lines 1-5). Furthermore, Kuna, *et al* teach the dosage should be in the range of about 0.5 to 500 μ g/kg, preferably 20 to 200 μ g/kg (pg 24, lines 14-15). Kuna, *et al* do not teach the administration of MIG as the cytokine and do not teach the chemoattractant to be inhibited.

Loetscher, *et al* teach that MIG and IP-10 are expressed on Th₁ cells while CCR3, the receptor for eotaxin and several other CC chemokines is characteristic of Th₂ cells. MIG and IP-10 compete for binding of eotaxin to CCR3-bearing cells and inhibit migration and Ca²⁺ changes induced in such cells by eotaxin and eotaxin-2 (pg 2986, Abstract). Loetscher, *et al* teach that eotaxin is expressed in a wide variety of cells, including eosinophils, lymphocytes, macrophages, and endothelial and epithelial cells, and is critically involved in the regulation of the basal and inflammation-dependent traffic of eosinophils. In addition, Loetscher, *et al* teach that in eotaxin-deficient mice and in animals treated with antibodies that neutralize eotaxin, eosinophil infiltration of the

airways is markedly reduced (pg 2986, col 2). Loetscher, *et al* suggest that chemokine receptor blockade is a possible therapeutic approach for inflammatory diseases (pg 2989, col 1).

Kaplan teaches chemokines which are chemotactic for eosinophils include eotaxins I, II and III and that CCR3 is required (pg 428, col 2). Kaplan teaches that in allergic late-phase responses, eotaxin has been associated with the early accumulation of eosinophils and in the skin, eotaxin II and MCP-4 have been associated with tissue eosinophilia (pg 429, col 2). In addition, Kaplan teaches that basophils and eosinophils are present in late-phase reactions of the nose, lung and skin and may perpetuate allergic inflammation by virtue of their local activation and secretion (pg 429, col 1). Kaplan also teaches that targeting the CCR3 receptor would be a therapeutic goal because eotaxins, MCP-3, MCP-4 and RANTES functions via this receptor.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to inhibit eosinophilia or eosinophil recruitment and alleviate symptoms of inflammation or allergic response because eosinophils accumulate in allergic late-phase responses by administering MIG via intranasal inhalation in the effective dosage range as taught by Kuna, *et al* because it is the preferred method of administration. The person of ordinary skill in the art would have been motivated to administer MIG to block CCR3 thereby preventing eosinophilia. Moreover, the person of ordinary skill in the art would have a reasonable expectation of success because MIP and IP-10 competes for binding of eotaxin to CCR-3 on eosinophils.

Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kuna, *et al* (WO9421277) in view of Loetscher, *et al* (J. Biol. Chem. 276(5): 2986-2991, 2001) as applied to claims 1-5, 14-19, 31-33, and 44-50 above and further in view of Bates, *et al* (J. Biol. Chem. 275: 10968-10975, 2000).

The claimed invention is drawn to a method of inhibiting at least one of eosinophil recruitment or function wherein ERK-1 or ERK-2 is perturbed, by administering an isolated cytokine such as MIG or IP-10 with eosinophil recruitment- or function-inhibitory activity in a pharmaceutically effective amount.

As set forth *supra*, Kuna, *et al* teach a method of inhibiting allergic disease, e.g. a respiratory allergic disease in mammals such as humans by administering a therapeutically effective amount of one or more of RANTES, MIP-1 α , MIP-1 β , CTAP-III or IP-10 (pg 7, lines 24-30). Kuna, *et al* teach the treatment of allergic diseases such as asthma by administration via various routes.

Loetscher, *et al* teach that eotaxin is expressed in a wide variety of cells, including eosinophils, lymphocytes, macrophages, and endothelial and epithelial cells, and is critically involved in the regulation of the basal and inflammation-dependent traffic of eosinophils and that MIG and IP-10 compete for binding of eotaxin to CCR3-bearing cell (pg 2986, Abstract). Loetscher, *et al* suggest that chemokine receptor blockade is a possible therapeutic approach for inflammatory diseases and that I-TAC, MIG and IP-10 are potent antagonists for CCR3 and prevent the responses of eosinophils and Th2 cells to CCR3-binding chemokines (pg 2989, col 1). Neither Kuna, *et al*. nor Loetscher, *et al*. teach that the signal transduction kinase, such as Erk-1 or Erk-2 is perturbed.

Bates, *et al* teach that eosinophils are the major effector cells contributing to allergic inflammation and asthma and eosinophilia and elevated levels of IL-5 are characteristic of asthma (pg 10968, col1). Bates, *et al* teach that one consequence of converging signals from cytokine and chemotactic factor receptors is the potent, rapid and transient stimulation of Erk-1 and Erk-2 activity (pg 10973, col 1). In addition, Bates, *et al* teach that in eosinophilia, priming with IL-5 and GM-CSF enables the cells to respond to chemotactic factors fMLP, IL-8 and RANTES with a rapid and vigorous activation of Erk-1 and Erk-2 (pg 10973, col 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer MIG or IP-10 to inhibit the activity of eotaxin on eosinophils as taught by Kuna, *et al.* and Loetscher, *et al* in order to perturb the signal transduction function as taught by Bates, *et al*. The person of ordinary skill in the art would have been motivated to prevent eosinophilia which is characteristic of asthma and allergy by down-regulating Erk-1 or Erk-2 stimulation. In addition, person of ordinary skill in the art would have a reasonable expectation of success for treating asthma or allergic symptoms because preventing eosinophilia in the lungs or pulmonary tissue would alleviate the symptoms of asthma or allergic response.

Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kuna, *et al* (WO9421277) in view of Loetscher, *et al* (J. Biol. Chem. 276(5): 2986-2991,2001) and Schmid-Grendelmeier *et al* (J. Immunol. 169: 1021-1027, 2002).

The claimed invention is drawn to a method for alleviating asthma in a patient comprising administering MIG thereby inhibiting IL-13-associated asthmatic response in the patient.

As set forth *supra*, Kuna, *et al* teach a method of inhibiting allergic disease, e.g. a respiratory allergic disease in mammals such as humans by administering a therapeutically effective amount of one or more of RANTES, MIP-1 α , MIP-1 β , CTAP-III or IP-10 (pg 7, lines 24-30). Kuna, *et al* teach the treatment of allergic diseases such as asthma by administration via various routes. Kuna, *et al* do not teach IL-13 is associated with an asthmatic response.

As set forth *supra*, Loetscher, *et al* teach that eotaxin is expressed in a wide variety of cells, including eosinophils, lymphocytes, macrophages, and endothelial and epithelial cells, and is critically involved in the regulation of the basal and inflammation-dependent traffic of eosinophils and that MIG and IP-10 compete for binding of eotaxin. Loetscher, *et al* teach that chemokine receptor blockade is a possible therapeutic approach for inflammatory diseases and that I-TAC, MIG and IP-10 are potent antagonists for CCR3 and prevent the responses of eosinophils and Th₂ cells to CCR3-binding chemokines (pg 2989, col 1

Schmid-Grendelmeier *et al* teach that IL-13 is an immunoregulatory and effector cytokine in allergic diseases such as bronchial asthma (pg 2986, Abstract). Schmid-Grendelmeier *et al* teach that eosinophils from patients suffering from bronchial asthma, atopic dermatitis, parasitic infections, hypereosinophilic syndrome, and idiopathic eosinophilic esophagitis expressed IL-13. In addition, Schmid-Grendelmeier *et al* teach

IL-13 expression in eosinophils under in vivo conditions (pg 2986, Abstract). Schmid-Grendelmeier *et al* teach that IL-13 can be released from eosinophils by eotaxin stimulation (pg 1026, col 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer MIG to inhibit the activity of eotaxin on eosinophils as taught by Loetscher, *et al.* in order to downregulate IL-13 release from eosinophils. The person of ordinary skill in the art would have been motivated to downregulate IL-13 because it is an effector cytokine released by eosinophils in allergic diseases.

Claims 1and 2 are rejected under 35 U.S.C. 103(a) as being obvious over Loetscher, *et al* (J. Biol. Chem. 276(5): 2986-2991, 2001).

The claimed invention is drawn to a method of inhibiting at least one of eosinophil recruitment or function selected from the group consisting of receptor expression, receptor internalization, signal transduction, transmigration, desensitization, degranulation, mediator release, oxidase activity and combinations thereof, by administering an isolated cytokine with eosinophil recruitment- or function-inhibitory activity in a pharmaceutically effective amount.

Loetscher, *et al* teach that MIG and IP-10 are expressed on Th₁ cells while CCR3, the receptor for eotaxin and several other CC chemokines is characteristic of Th₂ cells. MIG and IP-10 compete for binding of eotaxin to CCR3-bearing cells and inhibit migration and Ca²⁺ changes induced in such cells by eotaxin and eotaxin-2 (pg 2986,

Abstract). Loetscher, *et al* teach that eotaxin is expressed in a wide variety of cells, including eosinophils, lymphocytes, macrophages, and endothelial and epithelial cells, and is critically involved in the regulation of the basal and inflammation-dependent traffic of eosinophils. In addition, Loetscher, *et al* teach that in eotaxin-deficient mice and in animals treated with antibodies that neutralize eotaxin, eosinophil infiltration of the airways is markedly reduced (pg 2986, col 2). Loetscher, *et al* suggest that chemokine receptor blockade is a possible therapeutic approach for inflammatory diseases and that I-TAC, MIG and IP-10 are potent antagonists for CCR3 and prevent the responses of eosinophils and Th2 cells to CCR3-binding chemokines (pg 2989, col 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer MIG in a pharmaceutical composition to inhibit the activity of eotaxin on eosinophils as suggested by Loetscher, *et al.*

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Betty Lee, Ph.D. whose telephone number is (571) 272-8152. The examiner can normally be reached on M-F 9 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1647

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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